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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/811,367	03/16/2001	Nobuaki Takahashi	021286/027 8719	6403

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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 06/02/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/811,367	TAKAHASHI ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 February 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-39,41-65,71 and 72* is/are pending in the application.

4a) Of the above claim(s) *1-39 and 41-64* is/are withdrawn from consideration.

5)☒ Claim(s) *65* is/are allowed.

6)☒ Claim(s) *71 and 72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-39, 41-65, 71 and 72 are pending.

2. Claims 1-39, and 41-64 stand withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

3. Claims 65 and 71-72, drawn to a method for inhibiting an NK or T cell expressed cell surface MAFA binding to a ligand on target cell using an anti-MAFA antibody, are being acted upon in this Office Action.

4. In view of the amendment filed 2/28/05, the following objection and rejection remain.

5. The specification stands objected to because the "ATCC ___" on page 5 lines 5-9, and page 7, lines 19-23 need to be filled out. The request to this objection be held in abeyance until notification of allowable subject matter is acknowledged.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 71-72 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for a method for inhibiting an NK or a T cell expressed cell surface Mast cell function associated antigen (MAFA) binding to a ligand on a target cell in vitro or ex vivo comprising the steps (a) providing an anti-MAFA antibody or an antigen binding fragment thereof that specifically binds to a MAFA polypeptide set forth in any of SEQ ID NO: 1, 3 or 5 wherein antibody binding to the MAFA inhibits the binding of NK or T cell expressed cell surface MAFA to the ligand on the target cell, (b) contacting the anti-MAFA antibody or the antigen binding fragment thereof that specifically binds to a MAFA on the NK cell or the T cell or the target cell *in vitro* or *ex vivo* in an amount sufficient to inhibit cell surface MAFA binding to its ligand on the target cell, the said method wherein the anti-MAFA antibody or the antigen binding fragment thereof binding to the MAFA expressed on the NK or T cells inhibits the

MAFA from generating an inhibitory signal to the NK or the T cell and the said method wherein the anti-MAFA antibody or antibody binding fragment thereof inhibits NK cell or T cell mediated cytotoxicity, **does not** reasonably provide enablement for a method for inhibiting an NK or a T cell expressed cell surface MAFA binding to a ligand on a target cell wherein binding of the anti-MAFA antibody or the fragment thereof to the MAFA expressed on the NK or T cells generates any "inhibitory signal" to the NK cell or the T cell that inhibits any "activity" of the NK or the T cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only MAFA from human, rat and mouse comprising SEQ ID NO: 1, 3 and 5, respectively. The specification discloses that antibody and the binding fragment thereof that binds to the extra-cellular domain of mouse MAFA on T cells or NK cells **inhibits** the cytotoxic activity of NK cells or T cells (page 29, and 31). The specification further discloses a method for enhancing the cytotoxic activity of NK cell using recombinant soluble MAFA (Fig 2, page 30).

The specification does not provide sufficient guidance as how to make any "anti-MAFA" that generates "inhibitory signal" and inhibits any and all activity of the NK or the T cells upon binding to the MAFA expressed on NK or T cells. There is insufficient guidance as to the immunogen without the amino acid sequence used by applicant to make any antibody mentioned above that would generate an "inhibitory signal" to the NK or the T cell that inhibit all activity such as NK cell or T cell mediated cytotoxicity or NK cell.

Kuby *et al*, of record, teach that antibody epitopes (B cell epitopes) are not linear and are comprised of complex three-dimensional array of scattered residues which will fold into specific conformation that contribute to binding (See Kuby 1994, page 94, in particular). Immunization

with a peptide fragment derived from a full-length polypeptide may result in **antibody specificity** that differs from the antibody specificity directed against the native full-length polypeptide. Without the specific amino acid residues, it is unpredictable to determine which undisclosed subsequence of *any* anti-MAFA antibody wherein the subsequence "comprises" an antigen binding site would have the same antibody specificity as an antibody generated from the full-length polypeptide.

Ngo *et al*, of record, teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (see Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

Abaza *et al*, of record, teach that even a single amino acid substitution outside the antigenic site can exert drastic effects on the reactivity of a protein with monoclonal antibody against the site (See abstract, in particular).

The specification on page 4 lines 6-11 discloses anti-MAFA antibody or the binding fragment thereof that binds to NK or a T cell expressed cell surface MAFA wherein the antibody binding to the NK or T cell expressed cell surface MAFA inhibits the **MAFA** from generating an inhibitory signal to the NK or the T cells. The specification does not disclose that the antibody itself generates an inhibitory signal to the NK or the T cells upon binding, much less the antibody inhibits any activity of NK or T cell. Further, there is insufficient working examples demonstrating that any anti-MAFA would generate an "inhibitory signal" to the NK or the T cell that inhibit all activity such as NK cell or T cell mediated cytotoxicity or NK cell or T cell mediated secretion of which cytokine for the claimed method.

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 2/28/05 have been fully considered but are not found persuasive.

Applicants' position is that amended claims the specification adequately enables claims 65, 71 and 72 as amended. The specification discloses antibodies that inhibit ligand binding to

NK or T cell expressed MAFA. For example, the specification discloses that pharmaceutical agents, which include antibodies (page 4, lines 1-4; see, also, page 10, lines 13-17, and page 13, lines 11-13) that bind to NK or T cell expressed cell surface MAFA can prevent or inhibit NK or T cell surface-expressed MAFA from binding to a MAFA ligand (page 3, lines 14-17; see, also, page 5, line 26, to page 6, line 5). The specification exemplifies such anti-MMA antibodies (e.g., 7851 and F10) that bind to MAFA, that inhibit MAFA from binding to a MAFA ligand, and that generate an inhibitory signal to the NK or the T cell that in turn inhibits an activity of the NK or the T cells (see, for example, page 7, lines 6-12; page 10, lines 20-21; and page 31, line 11, to page 32, line 5). The specification additionally discloses that, although not limited to a particular functional mechanism, the compositions and methods of the invention can be used to inhibit or block NK cell and T cell activities by mimicking the binding of a cell surface expressed MAFA polypeptide interaction with a ligand expressed on a target cell, and that methods of the invention can be used to inhibit NK cell and T cell activities by initiating or augmenting or stimulating the ability of cell surface expressed MAFA to transmit inhibitory signals to these cells (page 10, lines 1-17). Thus, in view of the specification, the skilled artisan would know anti-MAFA antibodies that bind to MAFA expressed on NK or T cells that inhibit ligand binding to NK or T cell expressed MAFA, and antibodies which generate an inhibitory signal to the NK or T cell thereby inhibiting an activity of an NK or T cell.

In response, the specification discloses only MAFA from human, rat and mouse comprising SEQ ID NO: 1, 3 and 5, respectively. The specification discloses that antibody and the binding fragment thereof that binds to the extra-cellular domain of mouse MAFA on T cells or NK cells **inhibits** the cytotoxic activity of NK cells or T cells (page 29, and 31). The specification further discloses a method for enhancing the cytotoxic activity of NK cell using recombinant soluble MAFA (Fig 2, page 30). The specification on page 4 lines 6-11 discloses anti-MAFA antibody or the binding fragment thereof that binds to NK or a T cell expressed cell surface MAFA wherein the antibody binding to the NK or T cell expressed cell surface MAFA inhibits the **MAFA** from generating an inhibitory signal to the NK or the T cells. The antibody does not generate any inhibitory signal to the NK or T cells that inhibits any activity of NK or T cells.

8. Claim 65 is allowed.

9. **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

11. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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May 27, 2005

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